The Use of Newer Antidepressants for Panic Disorder

Jack M. Gorman, M.D.

Antidepressants are frequently prescribed to treat panic disorder. Although tricyclic antidepressants and monoamine oxidase inhibitors both block panic attacks, they have many adverse effects such as orthostatic hypotension and weight gain. High potency benzodiazepines such as alprazolam are also efficacious but carry the risk of physical dependency. Data from research trials as well as clinical experience are accumulating to indicate that the serotonin selective reuptake inhibitors (SSRIs)—fluoxetine, fluvoxamine, paroxetine, and sertraline—and perhaps venlafaxine, which inhibits both serotonergic and noradrenergic reuptake, are useful antipanic medications. The possibility also exists that these newer antidepressants such as SSRIs and venlafaxine are superior in effectiveness to the previously available drugs and, when combined with cognitive-behavioral therapy, might provide the best treatment outcome for patients with panic disorder.

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Antidepressants have been the hallmark of antipanic medication therapy since Klein and Fink first showed the efficacy of imipramine in blocking panic attacks.[1] At nearly the same time, the effectiveness of monoamine oxidase inhibitors (MAOIs) in treating panic disorder was also reported.[2–4] Research and clinical experience subsequently showed that most of the tricyclic antidepressants, including imipramine, desipramine, nortriptyline, and clomipramine, stop panic attacks within approximately 4 weeks of treatment initiation. Clomipramine may be effective at doses lower than the other tricyclics.[5,6] Phenelzine, an MAOI, may be slightly more effective than imipramine.[7]

CONSIDERATIONS WITH TRICYCLICS, MAOIs, AND BENZODIAZEPINES

Tricyclics

Although tricyclic antidepressants are effective in treating panic disorder, they have clear disadvantages. Tricyclics are universally anticholinergic; they cause dry mouth, constipation, blurry vision, and urinary retention. Most cause weight gain. All slow cardiac conduction through the AV node, occasionally causing incomplete bundle-branch block or even first degree heart block. Finally, tricyclics cause orthostatic hypotension and tachycardia. Although neither of these effects is generally of medical significance in young and otherwise healthy individuals, dizziness and increased heart rate are frequently disconcerting to the panic patient who has come for treatment particularly out of fear of such somatic sensations.

Another concern about tricyclics is their effect on heart period variability. Normally, heart rate increases with inspiration and decreases with exhalation. This "respiratory sinus arrythmia" or heart period variability is normal and controlled by direct central nervous system input to the heart via the vagus nerve. Tricyclics decrease vagal tone to the heart and reduce heart period variability. Decreases in heart period variability have been associated with poorer outcome after myocardial infarction.[8] Although not proved, the possibility exists that chronic vagal blockade and reduction in heart period variability could have adverse cardiovascular consequences.

MAOIs

Although such cardiac effects are less striking with monoamine oxidase inhibitors, MAOIs also produce substantial orthostatic hypotension and weight gain. Further, the need for a tyramine-free diet to avoid hypertensive crisis mandates that MAOIs be reserved for treatment-refractory patients. Reversible MAOIs—drugs that do not produce irreversible inhibition of the enzyme—may be effective in treating panic disorder.[9,10] None is currently available in the United States, however.

From the Department of Psychiatry, College of Physicians and Surgeons of Columbia University and the New York State Psychiatric Institute, New York, N.Y.

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Reprint requests to: Jack M. Gorman, M.D., Department of Psychiatry, College of Physicians and Surgeons of Columbia University, 722 West 168th Street, New York, NY 10032.

High Potency Benzodiazepines

Problems with tricyclic and MAOI antidepressants appeared to be overcome when alprazolam was introduced as the first high potency benzodiazepine for the treatment of panic disorder. In fact, at the time of this writing, alprazolam and clonazepam are the only benzodiazepines officially indicated for the treatment of panic disorder by the U.S. Food and Drug Administration (FDA). Alprazolam has been shown to be as effective as imipramine and more effective than placebo in the treatment of panic disorder.[11] Interestingly, one study[12] showed that imipramine is more effective than alprazolam for patients with high rates of spontaneous panic attacks, particularly when the attacks involve respiratory symptoms. It is now clear that other high potency benzodiazepines besides alprazolam, including clonazepam and lorazepam, are effective in treating panic disorder.[13,14]

Benzodiazepines have few of the adverse side effects associated with tricyclics and MAOIs. They are not anticholinergic and do not produce orthostasis, cardiac conduction changes, or weight gain. Even patients with serious medical illness can generally tolerate them.

The main problem with benzodiazepines in the treatment of panic disorder is the risk of physical dependency. One study[15] showed that about 70% of patients who had panic disorder and were treated with alprazolam had a discontinuation syndrome, which usually involved anxiety and agitation, when they attempted to taper off the drug. The fear of being unable to easily discontinue medication causes understandable uneasiness in some patients with panic disorder, even after they are reassured that with slow tapering the withdrawal effects of benzodiazepines are uncomfortable but not medically serious. Recently, two studies[16,17] suggest that cognitive-behavioral psychotherapy may be useful in helping patients discontinue benzodiazepines.

SSRIs AND VENLAFAXINE

Against this background of successful treatment for panic disorder with medications that nevertheless have significant shortcomings, the recent introduction of drugs that potently inhibit presynaptic neuronal reuptake of the neurotransmitter 5-hydroxytryptamine (5-HT), or serotonin, has had a rapid impact on pharmacotherapy of panic disorder. Four of these drugs currently marketed in the United States are serotonin selective reuptake inhibitors (SSRIs)—fluoxetine, fluvoxamine, paroxetine, and sertraline—and one, venlafaxine, inhibits both serotonergic and noradrenergic reuptake. Because of their specificity for one or, at most, two neurotransmitter systems, these drugs lack most of the serious side effects of tricyclics and MAOIs. None of them produce cardiac conduction abnormalities or orthostatic hypotension. None are significantly anticholinergic. Although tapering is recommended when any of the five new drugs are discontinued, none of them produce physical dependency, and patients can always discontinue their use when it is desirable.

Data from research trials as well as experience from clinical use are accumulating rapidly to indicate that the SSRIs, and perhaps venlafaxine, are effective antipanic medications. At the time of this writing, the FDA has approved paroxetine and sertraline for panic disorder.

Fluoxetine

In an open clinical trial, Gorman et al.[18] showed in 1987 that fluoxetine is effective in blocking panic attacks. Twenty patients were entered in the 18-week trial, which followed a 1-week placebo lead-in. Four patients were placebo responders and did not receive fluoxetine. Of the 16 patients who did receive fluoxetine, 8 withdrew because of side effects. Seven of the 8 who completed the trial responded to fluoxetine.

The high number of dropouts in the Gorman et al. study is probably attributable to the high doses of fluoxetine that were used. Patients were started at 20 mg/day but were moved to 80 mg/day according to the protocol. It is now clear that panic disorder patients are extremely sensitive to the effects of antidepressant medications and should always be started at smaller doses than are commonly prescribed to patients who have depression or obsessive-compulsive disorder. In an interesting study, Louie et al.[19] compared patients who had both panic disorder and major depressive disorder with those who had major depressive disorder alone for their ability to tolerate dose increases of fluoxetine from 5 to 20 mg daily. Patients with comorbid panic and depression were less likely than those with depression alone to tolerate the higher doses. Of 27 patients who had panic disorder and depression, only 13 were able to tolerate 20 mg/day; 5 continued taking doses lower than 20 mg/day, and 9 dropped out entirely.

Consistent with this report is the experience reported by Schneier et al.[20] in which treatment with fluoxetine was started at 5 mg/day for most of 25 patients who had panic disorder. In this report, 19 of the 25 patients displayed moderate or marked improvement, and 12 attained complete panic-free status.

For panic disorder as for depression, the combination of a tricyclic antidepressant, particularly one like desipramine or nortriptyline that is selective for noradrenergic reuptake, and fluoxetine may be useful for patients refractory to one class of drug alone.[21] This combination must be done cautiously, however, because fluoxetine is a potent inhibitor of the 2D6 isoenzyme of the hepatic cytochrome P450 system, which results in a relative inability by the patient to metabolize tricyclic antidepressants and high blood tricyclic levels. When the combination of any SSRI and a tricyclic is employed, frequent cardiac and blood tricyclic level monitoring is essential.

Fluvoxamine

A number of studies have investigated the efficacy of fluvoxamine for the treatment of panic disorder. Westenberg and den Boer[22] compared fluvoxamine with the heterocyclic agent maprotiline in a double-blind trial involving 47 patients who had panic disorder. Subjects were treated with 50 mg t.i.d. of fluvoxamine for 6 weeks. Fluvoxamine was effective in treating panic disorder and significantly more effective than maprotiline. In the same report, these investigators also provided the details of a double-blind, placebo-controlled trial comparing fluvoxamine with a specific serotonin receptor antagonist, ritanserin. In this study, patients who had panic disorder were randomly assigned to receive 75 mg b.i.d. of fluvoxamine for 8 weeks. Fluvoxamine was superior to both ritanserin and placebo in blocking panic attacks.

Hoehn-Saric and colleagues[23] compared fluvoxamine with placebo in 50 patients with panic disorder, 37 of whom completed the trial. Most (78%) of these patients also had agoraphobia. Eleven of the 18 randomly assigned to fluvoxamine became panic-free at the end of the 8-week study; fluvoxamine performed better than placebo on measures of overall disability, global measures, and depression ratings. Side effects included drowsiness, headache, and dyspepsia.

In a much discussed study, Black et al.[24] compared fluvoxamine with cognitive-behavioral psychotherapy in a double-blind, placebo-controlled trial. Patients randomly assigned to fluvoxamine began taking 50 mg daily; dosages were increased to 200 mg/day for all patients and then to 300 mg/day for those not responding to the lower doses. Sixty-two of the 75 patients entered in the study also had agoraphobia. A 3-week, placebo lead-in was followed by 8 weeks of randomized treatment. The dropout rate was very low for pharmacologic studies: only 8% of subjects dropped out of the active drug and placebo cells, while 20% dropped out of the cognitive-behavioral therapy cell. Fluvoxamine proved superior to both psychotherapy and placebo on most outcome measures, including measures of the number of panic attacks, overall disability, global improvement, and depression. Overall, 81% of patients who received fluvoxamine became panic-free at the end of the trial.

The Black et al. study[24] has been criticized by cognitive and behavioral psychotherapists because an 8-week treatment period is relatively short for this kind of therapy and because the dropout rate appears to be high for psychotherapy treatments. Black et al. also reported on the results of withdrawing the patients from fluvoxamine treatment.[25] Fourteen patients who had panic disorder (13 with agoraphobia as well) who were receiving a mean dose of 236 mg/day of fluvoxamine for 8 months were abruptly withdrawn from the drug and observed for 2 weeks. A withdrawal reaction characterized by dizziness, incoordination, headache, irritability, and nausea began 24 hours after withdrawal, peaked in intensity at 5 days, and was mostly gone by Day 14. This study, plus numerous case reports of a withdrawal reaction after discontinuing SSRIs, has prompted the recommendation that SSRIs be tapered gradually after chronic treatment.

Finally, de Beurs et al.[26] randomly assigned 96 patients with panic disorder to one of four cells: fluvoxamine plus exposure therapy, placebo plus exposure, cognitive-behavioral psychotherapy plus exposure, and exposure alone. Doses of fluvoxamine ranged from 50 to 150 mg/day, and treatment lasted for 11 weeks. The study is somewhat difficult to interpret because of a relatively low number of panic attacks in the patients at baseline prior to beginning the study. This may explain the finding that no differences in reduction in the number of panic attacks were observed among the groups. However, fluvoxamine was significantly superior to all other treatments in decreasing phobias and in global improvement. Side effects to the drug were mild and included headache and sleeplessness.

Paroxetine

Large multicenter trials examining the effectiveness of paroxetine as an antipanic agent have now been reported. LeCrubier[27] compared paroxetine with the tricyclic drug clomipramine in a double-blind, placebo-controlled trial that involved 12 weeks of treatment after a 3-week placebo lead-in. Four hundred eighty patients were enrolled, of whom 368 were randomly assigned to study treatments; data for an intention-to-treat analysis are available for 367 subjects. Doses of paroxetine ranged from 10 to 60 mg daily, while those for clomipramine ranged from 10 to 150 mg daily. Paroxetine was superior to both clomipramine and placebo in reducing the number of panic attacks. Clomipramine had more side effects than paroxetine, but the number of adverse side effects reported for paroxetine was no greater than that reported for placebo.

Three different doses of paroxetine (10, 20, and 40 mg/day) were compared with placebo in a double-blind trial involving 278 patients treated for 10 weeks.[28] Statistically significant differences were observed between paroxetine at the 40-mg/day dose and placebo in the reduction of panic attacks, percentage of patients achieving panic-free status, and global severity score. Paroxetine was also superior to placebo in reducing phobias, depression, and overall anxiety.

In an interesting study, Oehrberg et al.[29] compared paroxetine with placebo; patients who were randomly assigned to both groups also received cognitive therapy for panic disorder. This is important because, given the effectiveness of cognitive and behavioral psychotherapy in treating panic disorder, it has often been hard to show a significant advantage of a medication over placebo when subjects are also getting psychotherapy. For this trial, patients were first placed on 10 mg/day of paroxetine, and

then the dose was increased to 20 mg/day. Further increases to a maximum of 60 mg/day were permitted if needed. Of the 129 patients enrolled, 9 were dropped as placebo responders during the 3-week lead-in, 120 were randomly assigned to a treatment group, and 107 completed the study. Most (N = 113) of the 129 enrolled patients also had agoraphobia. Despite the use of cognitive therapy for all patients, a significant advantage of paroxetine over placebo was still demonstrated for reduction in the number of panic attacks, global improvement, and decreases in scores on depression and anxiety scales. Side effects included nausea, sweating, headache, dizziness, asthenia, dry mouth, and decreased libido. Interestingly, after the drug was discontinued, no withdrawal effects were noted.

Sertraline

A multicenter study examining the effectiveness of sertraline in the treatment of panic disorder has also been reported.[30] Three hundred twenty patients with panic disorder were entered in a double-blind, placebo-controlled trial with three doses of sertraline: 50, 100, and 200 mg daily. Patients were treated for 12 weeks after a 2-week placebo lead-in. Sertraline proved superior to placebo on a clinical global improvement scale, by a reduction in number of panic attacks, and with an improvement in phobic avoidance and overall anxiety level.

The effectiveness of SSRIs in the treatment of panic disorder can be summarized with reference to a meta-analysis published by Boyer.[31] Twenty-seven studies involving 2348 patients were included in the analysis. Only studies using randomization, prospective design, double-blinds, and placebo-controls were entered into the meta-analysis. The effects sizes, a statistical measure of the amount of difference between an active intervention and a comparator (in this case, placebo), of the studies were compared. The results of the meta-analysis showed that the effects sizes for SSRIs, which in this report included fluvoxamine, clomipramine, paroxetine, and an experimental compound called zimelidine, were larger than those for imipramine or for alprazolam. This meta-analysis suggests that SSRIs not only have fewer potential adverse side effects than imipramine or alprazolam in the treatment of panic disorder, but may also be more effective antipanic agents.

Venlafaxine

The mechanism of action by which medication blocks panic attacks is still under investigation, but a coherent theory has emerged (for a review, see reference 32). Until SSRIs were introduced, all of the medications known to have antipanic efficacy had in common the property of decreasing brain noradrenergic activity, generally by reducing the firing rate of the central noradrenergic nucleus, the pontine locus ceruleus. SSRIs do not have a direct effect on the noradrenergic system, but increase overall brain serotonergic neurotransmission. However, preclinical studies indicate that increasing serotonergic function in the central nervous system leads to inhibition of the locus ceruleus and a decrease in noradrenergic activity. This has recently been shown in patients with panic disorder as well by Coplan et al.,[33] who demonstrated a decrease in the major noradrenergic metabolite, MHPG, in patients with panic disorder who had been successfully treated with the SSRI fluoxetine. Hence, the theory has emerged that antipanic medication therapy works by decreasing noradrenergic and increasing serotonergic function in the central nervous system.

Given this theoretical explanation for the antipanic effects of drugs, it follows that a medication capable of directly affecting both noradrenergic and serotonergic function may have an important ability to treat panic disorder. Given reports that patients with panic disorder who are refractory to SSRIs may then respond to the combination of an SSRI and a noradrenergically specific tricyclic drug, this idea becomes of even greater interest.

Venlafaxine inhibits reuptake of both norepinephrine and serotonin. Unlike tricyclic agents that also have this dual neurotransmitter action, however, venlafaxine is not anticholinergic and does not affect cardiac conduction, produce orthostatic hypotension, or cause weight gain. Research trials examining the antipanic effects of venlafaxine are now under way.

Recently, Geracioti[34] reported on the results of open treatment with venlafaxine of four consecutive panic disorder patients. Patients were started at very low doses—18.75 mg b.i.d. in three patients and 12.5 mg b.i.d. in the fourth—and titrated up to final doses of 50 or 75 mg/day. All four patients responded to venlafaxine. The drug had a rapid onset of action and produced few adverse side effects. It should be remembered, however, that this, to my knowledge, is the first published report of venlafaxine therapy for panic disorder and, as the author notes, requires replication and extension with appropriate experimental design before further conclusions can be drawn. An open study by Papp et al.[35] also suggests that venlafaxine is effective in the treatment of panic disorder.

CONCLUSION

In the past, adverse side effects have often been limiting factors in the treatment of patients with panic disorder. Some drugs, like the tricyclics, produce side effects that are reminiscent of actual panic symptoms, while the fear of physical dependency on benzodiazepines has been a deterrent to their use for some patients. The introduction of SSRIs and venlafaxine as potential antipanic medications may obviate many of these concerns. There is also the possibility that the SSRIs and venlafaxine are actually superior in effectiveness to the previously available drugs.

Attention must also be given to the possibility that the combination of medication with cognitive-behavioral psychotherapy might offer the best possible treatment outcome for patients with panic disorder.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others), maprotiline (Ludiomil), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for panic disorder: fluoxetine, MAOIs, TCAs, venlafaxine, and the combination of fluoxetine and a TCA.

Discussion

Dr. Keck: What is the latest interpretation of the risk of suicide in panic disorder? I have seen two or three reanalyses and have never decided if the association between panic disorder and suicide is real.

Dr. Gorman: Weissman et al. [New Engl J Med 1989; 321:1209–1214], in an analysis of data from the Epidemiologic Catchment Area (ECA) study, concluded that panic disorder and attacks are associated with an increased risk of suicidal ideation and suicide attempts. However, Hornig and McNally [Br J Psychiatry 1995;167:76–79], in a reanalysis of the same data, found the opposite: panic disorder was not associated with an increased risk for suicide attempt.

Dr. Hirschfeld: Results from the Collaborative Depression Study [Fawcett J, Scheftner WA, Fogg L, et al. Am J Psychiatry 1990;147:1189–1194] showed that the risk for completed suicide is increased in patients who have comorbid panic and depression. Long-term studies of patients with only panic disorder show no completed suicides.

Dr. Gorman: The comorbidity issue is critical. The ECA data show a 14-fold increase in suicide attempts in patients with complicated panic disorder and comorbid depression.

Dr. Keller: Data from the HARP study [Warshaw MG, Massion AO, Peterson LG, et al. J Affect Disord 1995;34: 235–247] associate the probability of suicide attempts with the presence and severity of depression in patients with panic disorder.

Dr. Gorman: In comorbid depression and panic disorder, the suicide rate is clearly elevated above the rate for panic disorder or depression alone, but data indicating that panic disorder without depression increases the suicide risk are weak.

Boyer, [Int Clin Psychopharmacol 1995;10:45–49] in a meta-analysis of studies involving more than 2000 patients, found the effect sizes for the available SSRI studies are larger than those for imipramine or alprazolam. The only caveat is that the meta-analysis includes not just fluvoxamine and fluoxetine but also zimelidine and clomipramine.

I agree that the hypersensitivity of panic patients to these drugs is extremely robust. If patients with panic disorder have a serotonin deficiency, a sudden infusion of serotonin in the synapse will lead to a denervation supersensitivity in the postsynaptic receptor. My own clinical experience is that starting patients at extremely low doses of SSRIs obviates the problems, and many physicians are beginning to use SSRIs as a first-line treatment.

Dr. Hirschfeld: There are several large studies on the acute treatment of panic disorder with SSRIs, sertraline, and paroxetine in particular. There is a maintenance study of paroxetine as well.

Dr. Yonkers: If you were to look at the published literature, you would find evidence for using clomipramine and fluvoxamine to treat panic disorder; the evidence for sertraline and fluoxetine has not yet been published. Considering the widespread use of these drugs for this disorder, the data are not in the literature.

Dr. Gorman: Dr. Yonkers, you are right if you base your decision on a MEDLINE search. Many studies are still unpublished because the pharmaceutical companies are holding the data. For example, I know of a double-blind, placebo-controlled, multicenter fluvoxamine study that has been submitted for publication. Although many of the data have not been published in refereed journals, the data have been submitted to the Food and Drug Administration (FDA) or been presented in public.

Dr. Hirschfeld: Are you suggesting that we shouldn't select a particular treatment until published data support the treatment?

Dr. Keck: My experience is that serotonin reuptake inhibitors are almost uniformly effective for patients who have panic disorder if treatment is started with a low dose that is titrated slowly. Clinical experience has made the use of these drugs for panic disorder widespread.

Dr. Gorman: After a pharmaceutical company secures FDA approval to market the drug for a particular disorder, the system provides no impetus for the company to engage in large clinical trials to secure FDA approval for other disorders since physicians will prescribe the agent for other conditions in which experience has proved it useful.